

PATENT COOPERATION TREATY

REC'D 02 AUG 2005

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/036492

International filing date (day/month/year)
03.11.2004

Priority date (day/month/year)
04.11.2003

International Patent Classification (IPC) or both national classification and IPC
A61K48/00, C12N15/87, C12N15/11

Applicant
THE UNITED STATES OF AMERICA AS REPRESENTED BY ...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, Inventive step and Industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 8-12, 19-23, 30-34

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said-claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 8-12, 19-23, 30-34
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- the written form ☐ has not been furnished
- ☐ does not comply with the standard
- the computer readable form ☐ has not been furnished
- ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-7, 13-18, 24-29 (all partially)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-6
Inventive step (IS)	Yes: Claims	
	No: Claims	7, 13-18, 24-29
Industrial applicability (IA)	Yes: Claims	1-7, 24-29
	No: Claims	13-18

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

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Re Item III.

- 1) The international search report has been drawn up in respect of the subject-matter of **Claims 1-7, 13-18, 24-29 (all partially)** of the international application. The present Examining authority will carry out a preliminary examination report only on the parts of the application for which an international search report has been established (Rule 66.1 (e) PCT).

Re Item IV.

- 2) The application as filed is considered to lack unity of invention since its subject-matter relates not to one but rather to 5 separate inventions not linked together by a common underlying inventive concept as required by Art. 3(4)(iii) PCT and Rule 13 PCT.

- 3) The claims and the inventions to which the 5 separate inventions relate may be grouped as follows:

INVENTION 1

Claims 1-7, 13-18, 24-29 (all partially): method for attenuating transmission or infection by an immunodeficiency virus by providing an inhibitor of p21 to a cell wherein said inhibitor is a polynucleotide comprising at least 10-contiguous nucleotides of SEQ ID NO:8; a method of treating AIDS by providing the same inhibitor; a pharmaceutical composition comprising the same inhibitor

INVENTION 2

Claims 1-7, 13-18, 24-29 (all partially): the same as Invention 1 but for SEQ ID NO:10

INVENTION 3

Claims 1-4, 8-10, 13-15, 19-21, 24-26, 30-32 (all partially): the same as Invention 1 but for SEQ ID NO:7

INVENTION 4

Claims 1-4, 8-10, 13-15, 19-21, 24-26, 30-32 (all partially): the same as Invention 1 but for SEQ ID NO:9

INVENTION 5

Claims 11, 12, 22, 23, 33, 34 (all entirely); 1-4, 13-15, 24-26 (all partially): the same as Invention 1 wherein said inhibitor is 2-cyano-3, 12-dioxooleana-1,9-dien-28-

oic acid (CDDO)

- 4) According to Rule 13 PCT, an international patent application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features. Special technical features are such features that define the contribution of the claimed invention over the prior art.

The identified 5 inventions relate to " methods for reducing HIV infectivity" involving the technical feature of "treatment of a cell with an inhibitor of p21" as the sole common link. However, this feature cannot be accepted to constitute a special technical feature because it does not define a contribution over the prior art. A method for increasing HIV induced cell death by treatment with antisense p21 nucleotides is already known in the art (see the document cited in the application, "Cytoplasmic p21 WAF1/Cip1 protects U937 promonocytic cells from HIV mediated apoptosis" poster 278-T presented in 9th Conference on retroviruses and opportunistic infections, February 2002).

- 5) The contributions claimed in the present application which are allegedly made over the prior art are:
- 1) a p21 inhibitor which comprises at least 10 contiguous nucleotides of SEQ ID NO:8
 - 2) a p21 inhibitor which comprises at least 10 contiguous nucleotides of SEQ ID NO:10
 - 3) a p21 inhibitor which comprises at least 10 contiguous nucleotides of SEQ ID NO:7
 - 4) a p21 inhibitor which comprises at least 10 contiguous nucleotides of SEQ ID NO:9
 - 5) a p21 inhibitor which is triterpenoid 2-cyano-3, 12-dioxooleana-1,9-dien-28-oic acid (CDDO)

These contributions are not so linked as to form one single inventive concept.

Re Item V.

- 6) The present application discloses the finding that HIV infection of macrophages induces expression of a gene encoding cyclin-dependent kinase inhibitor p21 (also known as Waf1, Cip1, CDKN1A). This protein is assumed to be implicated in protecting macrophages from HIV-induced apoptosis thus, creating a reservoir of virus which furthers infection. Antisense polynucleotides and small interfering RNAs (siRNA) recognizing parts of p21 reduce viral infection (Figure 6). The same effect is noticed after treatment with the triterpenoid 2-cyano-3, 12-dioxooleana-1,9-dien-28-oic acid (CDDO) (Figure 5) which is known to regulate expression of p21.
- 7) The following documents are referred to in the present communication. The numbering will be adhered to for the rest of the procedure:
- D1: GOMEZ ET AL.: "Cytoplasmic p21 WAF1/Cip1 protects U937 promonocytic cells from HIV mediated apoptosis"[Online] 24 February 2002 (2002-02-24), - 28 February 2002 (2002-02-28) Retrieved from the Internet:
URL:WWW.RETROCONFERENCE.ORG/2002/POSTERS/1_3446.PDF>
[retrievable from 2002-05-24 on]
- D2: WO 01/88191 A (THE UNITED STATES OF AMERICA AS REPRESENTED BY THE DEPARTMENT OF VETER) 22 November 2001 (2001-11-22)
- D3: KAWATA SANAE ET AL: "p21Waf1/Cip1/Sdi1 prevents apoptosis as well as stimulates growth in cells transformed or immortalized by human T-cell leukemia virus type 1-encoded Tax." JOURNAL OF VIROLOGY, vol. 77, no. 13, July 2003 (2003-07), pages 7291-7299.
- 8) The subject-matter of **Claims 1-6** is not novel as required by Article 33(2) PCT.

Document D1 discloses the generation of U937-cells stably transformed to express a p21 antisense nucleotide. Said cells were infected with HIV and it was shown that following HIV infection, p21 up regulation was suppressed and that said cells were significantly more susceptible to HIV-induced cell death than the control U937 cells. It follows that said cells are not capable to transmit the virus as much as the control U937 cells.

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- 9) The application does not disclose the use of antisense nucleotides comprising 10 contiguous nucleotides of SEQ ID NO:8 (nor SEQ ID NO:10 for that matter). As such, it remains speculative whether the subject-matter of **Claim 7** solves the technical problem set in the application. Therefore, the inventiveness of the subject-matter of **Claim 7** cannot be acknowledged as required by Article 33(3) PCT.

The same applies to **Claims 13-18, 24-29**.